

## CONTEXT

Cost-effectiveness analyses in oncology often require indirect survival comparisons whenever several comparators are implied and there are no comparative studies which directly evaluate their relative efficacy. Bayesian network meta-analysis (NMA) is a standard method to gather different efficacy data into one single comparison via hazard ratios estimation. However, this approach relies on the validation of the proportional hazards assumption (PHA) for each source. If the assumption is violated, Bayesian NMA can not be applied. Therefore, alternative NMA models should be used, such as fractional polynomials.

## OBJECTIVES

To apprehend current uses of these alternative methods and their acceptability on economic studies, our study reviewed all dossiers submitted to the French Health Authority (HAS) in which NMA were used, and the proportional hazards assumption discussed.

## METHODS

We conducted a retrospective analysis of all HAS efficiency opinions published from January 1st, 2020 up to January 1st, 2023, focusing on methodologies submitted and HAS associated methodological reservations.

## RESULTS

Among the 76 dossiers submitted, 14 used network meta-analysis to measure relative efficacy of treatments and comparators (see Table 1). 12 of these 14 dossiers were submitted for an indication in oncology. PHA validity was demonstrated in only four cases, through Schoenfeld residuals test and/or residuals visual inspection. When the PHA was violated and Bayesian NMA was not used, the methods selected were fractional polynomials (five times) and the method proposed by Ouwers et al. (twice). One study proposed several sensitivity analyzes in addition to PHA scenario, leading to an important reservation from HAS. Four major reservations were raised by the HAS, and important reservations were given to two other dossiers.

### Bayesian NMA

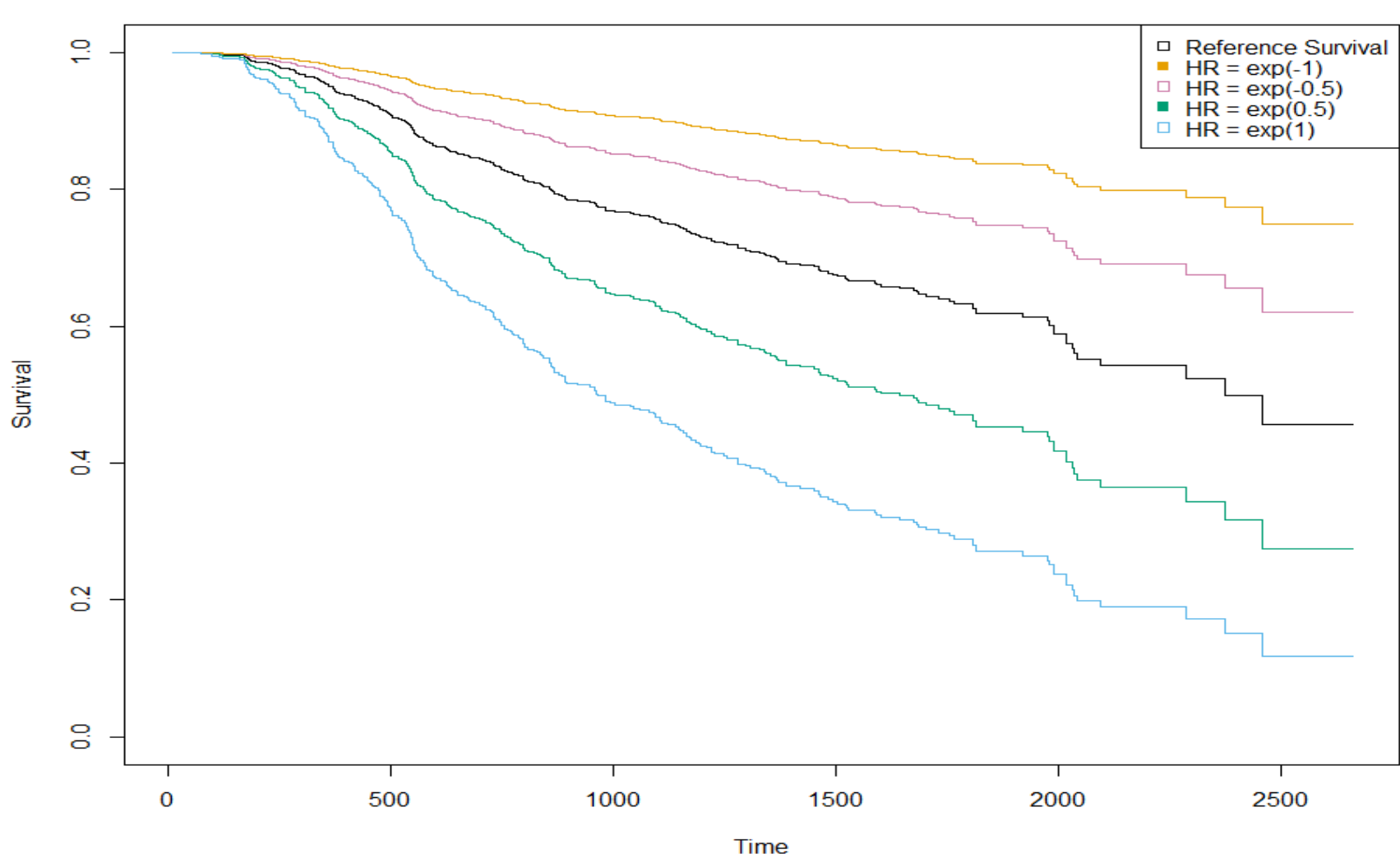
A reference treatment (often placebo when available) is determined. Then, Bayesian NMA allows to estimate the coefficient  $\alpha_i$  such as, for every treatment  $i$ , at every time  $t$ :

$$\frac{\lambda_i(t)}{\lambda(t)} = \alpha_i$$

Where  $\lambda_i(t)$  is the hazard function for treatment  $i$  and  $\lambda(t)$  is the hazard ratio for the reference treatment.  $\alpha_i$  is called the hazard ratio for treatment  $i$  and is constant from time to time, implying the hypothesis of proportional hazards.

Figure 1 shows an example of survival curves obtained with proportional hazards assumption. The survival reference was obtained with data file GBSG from package mfp in R.

FIGURE 1: Example of survival curves in the Bayesian NMA framework



### Fractional Polynomials

A reference treatment (often placebo when available) is determined. Then, for every treatment  $i$  used in the NMA, the hazard function  $\lambda_i(t)$  is computed through the following formula at second order:

$$\ln(\lambda_i(t)) = a_{0i} + a_{1i} * t^{p1} + a_{2i} * t^{p2}$$

With  $p1$  and  $p2$  included in  $\{-2; -1; -0.5; 0; 0.5; 1; 2; 3\}$  and  $t^0 = \ln(t)$ . For a first-order equation, the parameter  $a_{2i}$  is set to 0 for all  $i$ . This approach allows to fit a wide range of shapes for hazard functions, and enables survival curves to cross.

An example of survival curves obtained through this method is shown in Figure 2. Here,  $p1$  and  $p2$  are fixed to -1 and 1 respectively.

FIGURE 2: Example of survival curves with fractional polynomials

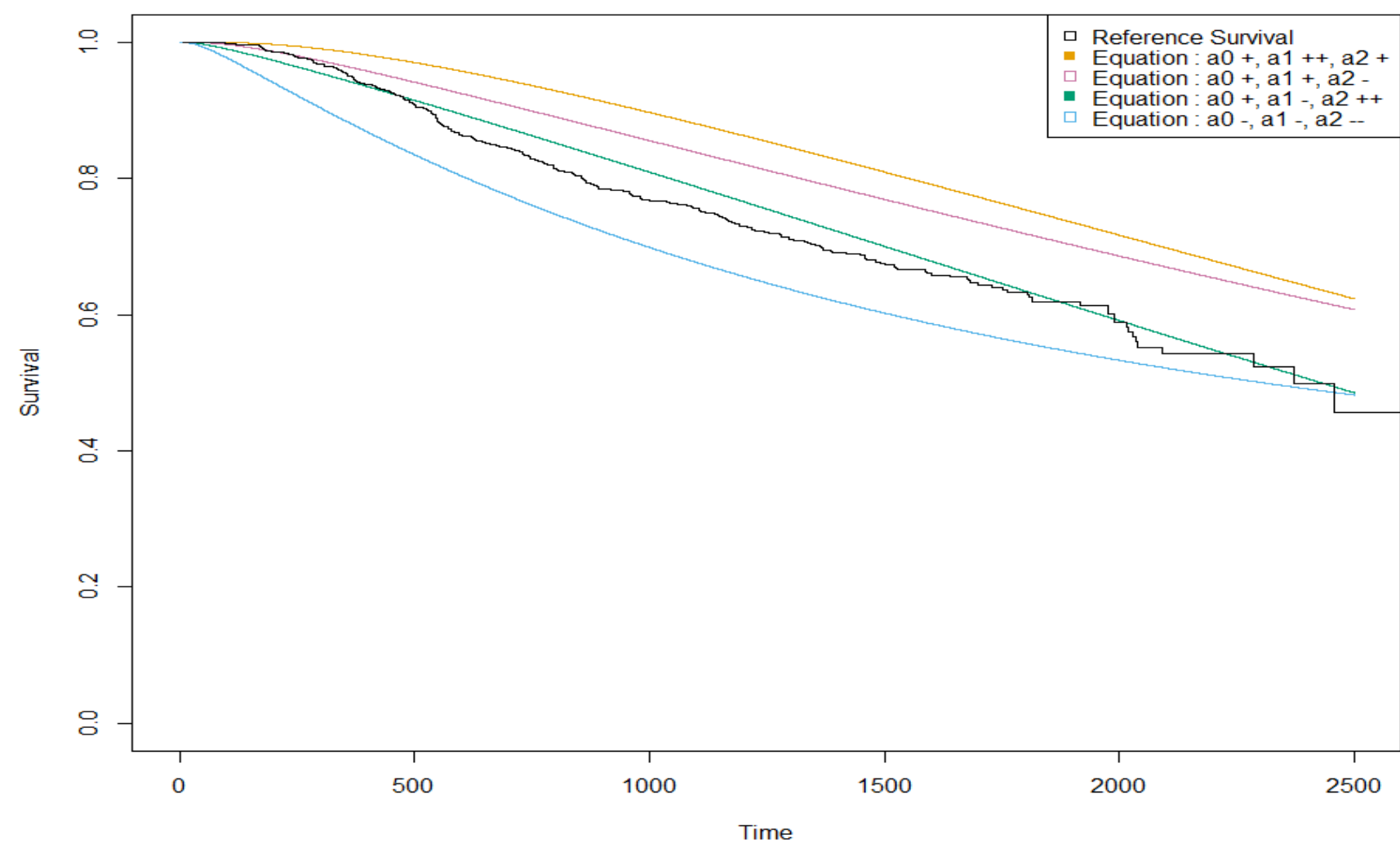


TABLE 1: Information about submitted dossiers with network meta-analysis

Brand name	International name of medicine	Pathology	Date of Publication
KEYTRUDA	pembrolizumab	Melanoma	December 2022
KAFTRIO	elexacaftor/tezacaftor/ivacaftor	Cystic fibrosis	October 2022
KISPLYX	lenvatinib	Renal carcinoma	July 2022
OPDIVO	nivolumab	Adenocarcinoma of the stomach, esophagogastric junction or esophagus	June 2022
MINJUVI	tafasitamab	Falling or refractory diffuse large B-cell lymphoma	April 2022
OPDIVO	nivolumab	Unresectable malignant pleural mesothelioma	March 2022
CABOMETYX	cabozantinib	Advanced renal cell carcinoma in adults	December 2021
LIBTAYO	cemiplimab	Locally advanced or metastatic non-small cell lung cancer	December 2021
OPDIVO	nivolumab	Advanced renal cell carcinoma	December 2021
TUKYSA	tucatinib	Breast cancer	July 2021
KESIMPTA	ofatumumab	Relapsing multiple sclerosis (RRMS)	June 2021
CALQUENCE	calquence	Chronic lymphocytic leukemia (CLL)	April 2021
ERLEADA	apalutamide	Metastatic hormone-sensitive prostate cancer (mHSPC)	July 2020
KEYTRUDA	pembrolizumab	Renal cell carcinoma (1st line)	March 2020

FIGURE 3: Methods used to model NMA survival curves

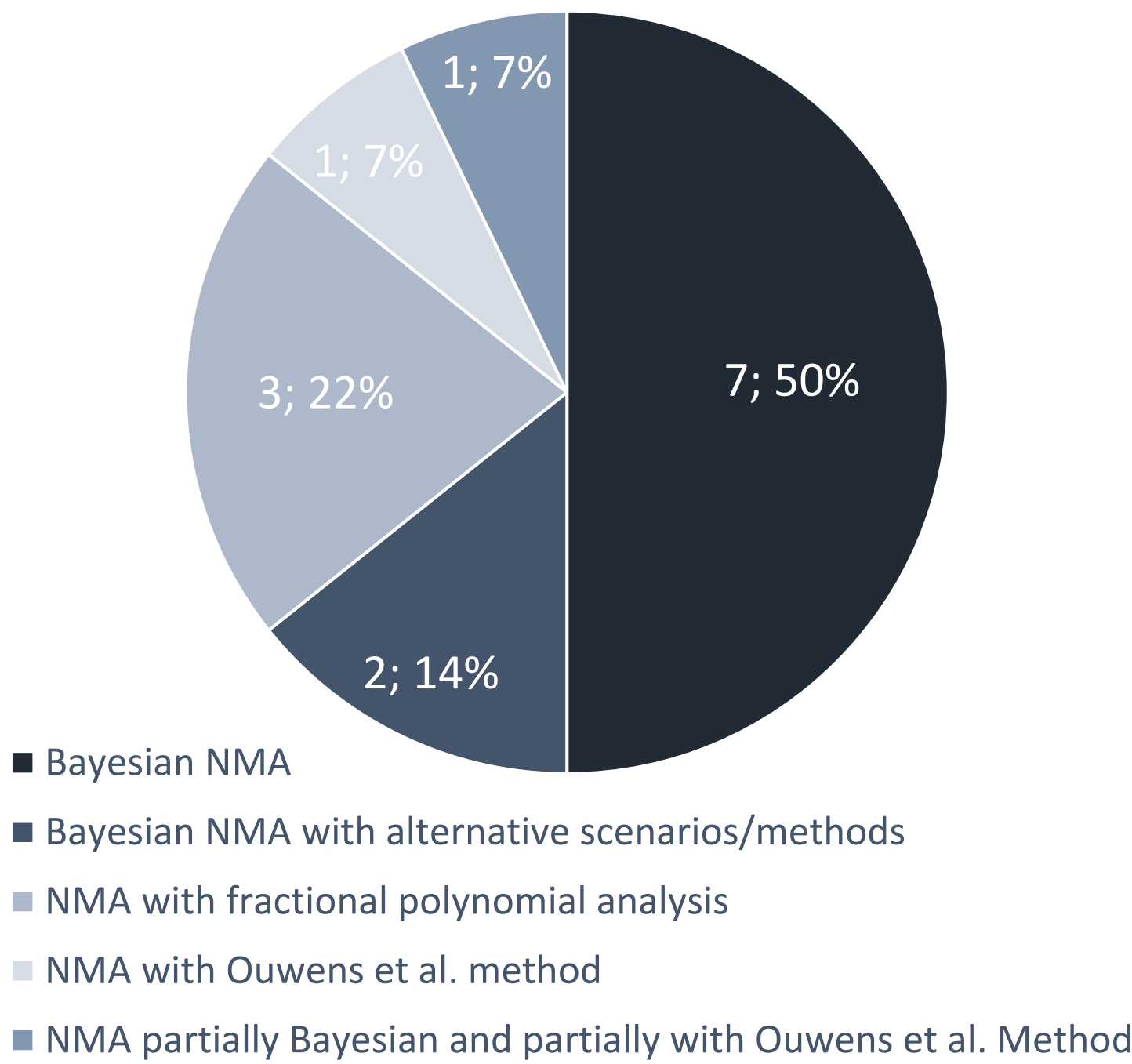
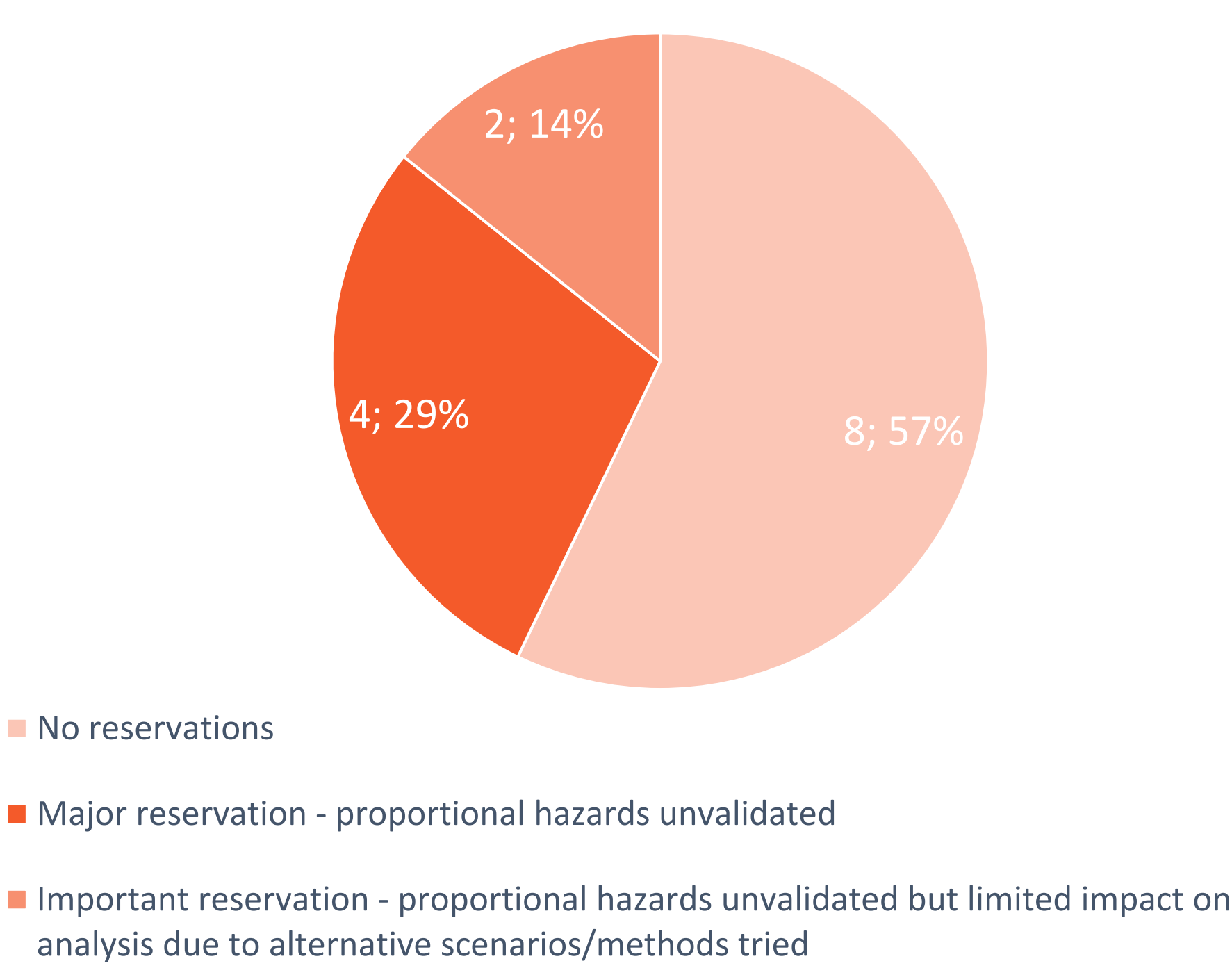


FIGURE 4: HAS Reservations about efficacy analyses



## DISCUSSION

- Assessing Bayesian NMA relevance is a mandatory step in economic evaluations. The use of Bayesian NMA without a rigorous check of the PHA and sufficient sensitivity analyses always led to a major reservation by the HAS.
- In the economic opinions studied, both fractional polynomials and Ouwers et al. method were considered valid by the HAS, highlighting the acceptability of these methods when the PHA does not hold.

## CONCLUSION

PHA validity would seem only occasional in network meta-analysis, and hazard-ratio adjustment methods remain underused. Clear guidelines on the use of these methods would be useful and could benefit to all stakeholders considering the diversity of possible approaches (fractional polynomials, Royston-Parmar model, piecewise exponential model...).

**COI:** KIRION J, ALAOUI E, ROBERT J and BAFFERT S are employees at CEMKA, one of the first French consulting firms in the field of evaluation of products, programs and organizations in Health. The study was not sponsored.

### REFERENCES

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- Ouwers M. et al., Network meta-analysis of parametric survival curves, doi: [10.1002/irsm.25](https://doi.org/10.1002/irsm.25), 2010 Jul..

